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Assessment of the effects of lacosamide on sleep parameters in healthy subjects

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ABSTRACT

Purpose: Seizures and antiepileptic drugs (AED) may disrupt sleep patterns in patients with epilepsy, thus evaluation of lacosamide effects on objective and subjective sleep measures is warranted.
Methods: A multicenter, interventional, open-label study (NCT01530386) was conducted in healthy subjects without confounding effects of concomitant AED use, co-morbidities, or disease state to determine whether lacosamide impacts sleep parameters after 22 days of lacosamide exposure. After overnight polysomnography (PSG) to assess baseline parameters, lacosamide was initiated at 100 mg/day (50 mg twice daily) and increased by 100 mg/day weekly to 300 mg/day (the mid-range maintenance dose for adjunctive therapy). The primary variable was change from baseline to post-treatment in wake after sleep onset (WASO). Secondary variables included additional objective sleep measures, subject-reported measures of sleep quality, daytime sleepiness, and tolerability. Change from baseline in WASO was analyzed using the Wilcoxon rank-sum test.
Results: A total of 27 subjects received ≥1 dose of lacosamide and 25 subjects completed the study. For WASO, median change from baseline was a 6-min reduction (95% confidence interval: −38, 77.5; $p = 0.1074$) after lacosamide treatment; this was considered not clinically relevant. No clinically relevant changes were observed in any secondary variables. Thirteen subjects (48%) reported a treatment-emergent adverse event, none of which was severe or led to study discontinuation.
Conclusion: Lacosamide 300 mg/day had no effect on objective or subjective sleep parameters in healthy subjects and was generally well tolerated.

1. Introduction

A complex relationship exists between epilepsy and sleep. Seizure activity is often associated with specific phases of the sleep/wake cycle, and sleep deprivation can precipitate seizure activity.[1,2] Inadequate or fragmented sleep, excessive daytime sleepiness, and decreased quality of life are often reported by patients with epilepsy and may be due to the presence or occurrence of seizures. Many antiepileptic drugs (AED) influence sleep parameters [2–9] and sleep architecture.[10] Negative effects on sleep associated with some AEDs include an increased percentage of light sleep, and reduced rapid eye movement (REM) and/or slow wave sleep (Stage 3).[7,11–13] AEDs may also cause daytime somnolence, fatigue, or drug-induced insomnia.[2,7,11–14] Since sleep disturbances significantly impair quality of life in patients with epilepsy,[15,16] formal assessment of the effects of AEDs on sleep parameters in individuals with and without epilepsy helps to identify any drug-induced impact on sleep and distinguish drug effects from a variety of medication and disease-related confounding factors. In addition, a better understanding of the effects of AEDs on sleep parameters may provide clinicians further information necessary for optimal AED selection.[1] Hence, a formal evaluation of the effects of lacosamide on sleep parameters was conducted in this study with healthy individuals.

Lacosamide is approved for monotherapy and adjunctive therapy of partial-onset seizures in patients 17 years of age and

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older in the US and as adjunctive therapy in adult and adolescent (16–18 years of age) patients in the European Union.[17,18] The recommended maintenance dose is 200–400 mg/day for adjunctive therapy and the World Health Organization daily defined dose is 300 mg/day.[19] Lacosamide acts via a novel mechanism of action, through selective enhancement of slow inactivation of voltage-gated sodium channels.[20,21] Efficacy and tolerability of lacosamide as adjunctive AED treatment was demonstrated in 3 pivotal Phase 2b/3 studies.[22–24] The most frequently reported treatment-emergent adverse events in these studies were associated with the central nervous system (dizziness and headache) and gastrointestinal tract (nausea), while fatigue and somnolence were reported at lower rates across doses of 200–600 mg/day.[22–24] To date, effects of lacosamide on sleep have not been formally assessed via objective assessment such as polysomnography (PSG); therefore, this study sought to evaluate whether lacosamide has any impact on objective and subject-rated measures of sleep.

Evaluating the effects of AEDs on sleep in healthy subjects has the benefit of distinguishing drug effects on sleep with fewer confounding variables. These individuals, unlike patients with epilepsy, do not take concomitant AEDs, experience seizures, or have co-morbidities that could affect sleep parameters. This evaluation was conducted in healthy subjects utilizing overnight PSG (7–8 h). The primary objective was to evaluate the effects of lacosamide 300 mg/day (the mid-range approved dose) on wake after sleep onset (WASO) in healthy subjects after 3 weeks of exposure. Secondary objectives included evaluating the effect of lacosamide on additional objective sleep measures, subject-reported measures of sleep quality, and tolerability.

2. Materials and methods

This was an open-label study conducted at 3 clinical sites in the US (ClinicalTrials.gov identifier: NCT01530386; SP1031). This study was conducted in accordance with the applicable regulatory and International Conference on Harmonisation Good Clinical Practice requirements and local laws. All subjects provided written informed consent prior to participation in the study.

2.1. Subjects

Healthy men and women aged 18–50 years with body weight (body mass index [BMI] $\geq$18 kg/m^2 and $\leq$28 kg/m^2) and good sleep hygiene with normal bedtime between 9:00 PM and 1:00 AM were eligible for inclusion. Subjects had no clinically relevant cardiovascular, renal, gastrointestinal, hepatic, metabolic, endocrine, neurological, or psychiatric abnormalities, and were in general good health.

Key exclusion criteria were history of or a PSG during screening revealing primary sleep disorders such as sleep apnea syndrome (including moderate-to-severe obstructive sleep apnea or an apnea-hypopnea index [AHI] >8) or narcolepsy, have a known hypersensitivity to any component of lacosamide, or taking concomitant medications within 2 weeks prior to the first day of dosing (except non-steroidal anti-inflammatory drugs, oral contraceptives, and non-psychoactive supplements; short-term use of medications for symptomatic relief was permitted but not within 3 days prior to the PSG). In addition, subjects who were smokers, had a history of alcohol or drug abuse or test positive on alcohol breath test or urine drug screen, were pregnant or nursing, or consumed >400 mg of caffeine/day or 40 g alcohol/day; had clinically relevant hematology or clinical chemistry parameters, physical examination or vital signs, or cardiac condition; or had a lifetime history of suicide attempt or suicidal ideation in the past 6 months, or any medical or psychiatric condition that, in the opinion of the investigator, could have jeopardized or would have compromised the subject's ability to participate in this study were excluded.

2.2. Study design

The study consisted of a screening period of up to 21 days, a 22-day treatment period, and a taper/safety follow-up. Screening was conducted over 3 visits: at Visit 1 (Day −21 [21 days before first administration of treatment]), subjects were evaluated for eligibility for enrollment into the study; Visit 2 (Day −2) consisted of the initial pre-treatment overnight PSG for an adaptation night of recording; and Visit 3 (Day −1) was the second pre-treatment overnight PSG followed by additional subjective sleep assessments the morning after as baseline sleep measurements.

Subjects began lacosamide treatment (Day 0) after completing the second pre-treatment overnight PSG during Visit 3. Lacosamide was provided as 50 mg and 100 mg tablets using the commercial formulation (UCB Pharma, Smyrna, GA). Tablets were taken in equally divided doses approximately 12 h apart, with the evening dose 2–3 h before bedtime. The initial dose was lacosamide 100 mg/day (lacosamide 50 mg twice daily) for 7 days, increased weekly by 100 mg/day to a target dose of lacosamide 300 mg/day [150 mg twice daily]). Dose reductions were not allowed; subjects who could not tolerate the lacosamide 300 mg/day dose were withdrawn.

After subjects had maintained a dose of lacosamide 300 mg/day for a period of 7 continuous days, Visit 4 (Day 21) was conducted, which included the first of the post-treatment overnight stays with PSG. On Visit 5 (Day 22), the second post-treatment overnight was conducted and subjects began a 2-day taper during which time they were to decrease the dose of lacosamide by 100 mg/day. Subjects returned for a safety follow-up at Visit 6 (Day 30).

2.3. Assessments

Overnight in-laboratory PSG recordings were conducted using standard methods for 7–8 h. Scoring of PSG tracings were performed in strict accordance with the criteria of the American Academy of Sleep Medicine Manual for Scoring Sleep by a central reader.[25,26] The international 10–20 electrode placement system was used for recording an electroencephalogram (ECG; F3, F4, C3, C4, O1, O2, M1, M2), electro-oculography (E1, E2), chin electromyogram, leg electromyogram, ECG, respiratory effort (chest and abdomen), pulse oximetry, and airflow (nasal pressure transducer and thermistor). Sleep staging, respiratory events (e.g., apneic events, hypopneic events), periodic limb movements, and arousals were scored at 30-s epochs on a high-resolution monitor. Hypopneas were scored according to rule VII.4.B (3%).[25]

Readings from the second night of the PSG were used for analysis. PSG recordings for the second overnight PSG assessment were initially scored by a certified scorer at the investigative site, so as to immediately determine the subject's eligibility to enroll in the treatment period of the study before they were sent to the central reader. Data from each first overnight assessment was considered as an adaptation to the sleep laboratory; therefore, sites were not required to score or send these files to the central reader for review unless the second overnight assessment was inadequate or not valid for evaluation.

The primary pharmacodynamic variable was change in WASO from baseline to the end of treatment as measured by PSG. WASO is a measure of sleep disruption and fragmentation, which may be associated with effect of seizures and medications in patients with epilepsy.[5,10] WASO was defined as the total time that was scored as awake in a PSG occurring between sleep onset and final wake up. Secondary PSG assessments were total sleep time (TST), sleep efficiency, percentage of sleep spent in each sleep stage (1, 2, 3, and

R),[25] latency to REM, sleep onset latency, latency to persistent sleep, arousal index (AI), AHI, and periodic limb movement index (PLMI) using standard accepted definitions.

Subject-rated pharmacodynamic variables were the Epworth sleepiness scale (ESS) and the Pittsburgh sleep quality inventory (PSQI); these assessments were collected following the second overnight PSG pre- and post-treatment. The ESS was used to evaluate daytime sleepiness, and ranges from 0 to 24, where higher scores indicate more sleepiness and scores 0–9 are considered normal.[27] The PSQI, which is used to assess sleep quality and disturbances, gives a global score (sum) of 7 components (each component has a range between 0 and 3 [overall global range: 0–21]; higher score indicates higher impairment, and scores >5 indicate poor sleep quality with severe difficulties in ≥2 components or moderate difficulties in >3 components).[28]

Tolerability was assessed by incidence of adverse events (including treatment-emergent adverse events and serious adverse events) that occurred during the study; subject withdrawal due to adverse events; changes in laboratory measurements, including hematology, clinical chemistry, and urinalysis parameters; changes in vital signs (including body weight); changes in 12-lead ECGs; suicidality (at screening as well as any suicidal ideation and behavior during the study) as assessed by using the Columbia-suicide severity rating scale[29]; and changes in neurological exam findings.

2.4. Analysis

Statistical analyses were performed using SAS version 9.13 (SAS Institute Inc., Cary, NC). Pharmacodynamic variables were evaluated for the full analysis set (all subjects who completed the PSG at baseline and end of the 3-week treatment). The planned analysis of the primary pharmacodynamic variable (change from baseline to end of treatment in WASO) was a paired *t*-test with a 2-sided significance of 0.05; however, results from 3 subjects indicated larger amounts of time spent awake during the PSG assessments compared with other subjects, although no procedural deviations were found. The resulting data was not normally distributed both at baseline and end of treatment; therefore, the planned *t*-test was not the most appropriate statistical test. A Wilcoxon rank-sum test was performed. Additionally, descriptive statistics on the percent change from baseline in WASO were calculated. For all secondary pharmacodynamic variables (sleep efficiency and TST), the 95% confidence interval (CI) around the median was calculated because of non-normally distributed data at both the baseline and end of treatment, and presented in addition to the planned 95% CI around the mean. For all other pharmacodynamic variables, only the planned 95% CI around the mean was presented. Safety outcomes were evaluated using the safety set (all subjects who received ≥1 dose of lacosamide).

It was prospectively estimated that a minimum of 19 subjects in the full analysis set would provide 90% power to detect a difference in means of 8.0 min in WASO, assuming a SD of the difference of 10.0 using a paired *t*-test with a 2-sided significance level of 0.05; this was based on findings of an 8 min difference in WASO between levetiracetam and carbamazepine in patients with epilepsy.[30] To adjust for potential drop outs, approximately 25 subjects were to be enrolled. No imputation of missing values for analysis parameters was performed.

3. Results

Disposition and baseline demographics for the 27 subjects who received ≥1 dose of lacosamide (safety set) are shown in Table 1. Baseline demographic characteristics of the 25 subjects who completed the study (full analysis set) were similar to the safety set. The majority of subjects followed the dose titration and tapering regimen; however, in 3 subjects, dose titration and tapering regimen differed from the administration regimen and 1 subject was consistently noncompliant in completing the drug dosing log.

Table 1
Subject disposition and demographics, safety set.

	All subjects (*N* = 27)
Disposition, *n* (%)	
Completed study	25 (92.6)
Discontinued	2 (7.4)
Reason for discontinuation	
Adverse event	1[a] (3.7)
Consent withdrawn	1 (3.7)
Demographics	
Age, years, median (range)	28.0 (18.0–48.0)
Male, *n* (%)	16 (59.3)
Race, *n* (%)	
Black	2 (7.4)
White	25 (92.6)
Ethnicity, *n* (%)	
Hispanic or Latino	2 (7.4)
BMI, kg/m^2, mean (SD)	23.6 (2.63)
Apnea-hypopnea index, median (range)	0.5220 (0, 4.377)

BMI, body mass index.
[a] One subject discontinued due to adverse events of increased alanine aminotransferase and aspartate aminotransferase at baseline. The subject had been treated with lacosamide 100 mg/day for 3 days prior to receiving information that baseline liver values were out of range.

3.1. Pharmacodynamic assessments

No clinically meaningful changes in sleep parameters were recorded with lacosamide 300 mg/day (Table 2). Median WASO decreased by 6 min (95% CI: −38, 77.5; 34.4% decrease) from baseline to end of treatment; this change was not statistically significant ($p = 0.1074$). Secondary pharmacodynamic variables of sleep efficiency, TST, and sleep latency also did not show any clinically relevant changes (Table 2). The percentage of time spent in stage 1 and stage 2 decreased slightly (by 0.38% and 2.37%, respectively), while the percentage of time spent in stage 3 and stage REM increased slightly (by 2.35% and 0.40%, respectively) after lacosamide treatment. No changes in AI, AHI, or PLMI were observed.

Mean values were in the normal range on the ESS and in the good sleep quality range on the PSQI at baseline, with no meaningful changes after lacosamide treatment (Table 2).

3.2. Safety and tolerability

Treatment-emergent adverse events were reported by 13 subjects (48.1%; Table 3). Twelve subjects (44.4%) had treatment-emergent adverse events that were considered drug-related by the investigator. The most common adverse events, each reported by 3 subjects (11.1%), were affect lability, headache, and somnolence. No deaths occurred.

All treatment-emergent adverse events were mild to moderate in severity. One subject experienced an adverse event of increased eosinophil count (no symptoms reported) that was initially classified as serious; however, none of the protocol-defined criteria for seriousness was met.

No subjects discontinued from the study due to adverse events related to lacosamide. One subject discontinued the study 3 days after initiation of lacosamide at 100 mg/day due to elevated alanine aminotransferase and aspartate aminotransferase reported on baseline safety assessments. This subject had received lacosamide 100 mg/day for 3 days prior to receiving the information that baseline liver values before starting lacosamide were out of range;

Table 2
Summary of changes in sleep parameters in healthy subjects before and after treatment with lacosamide 300 mg/day ($N = 25$, full analysis set).

Clinical and sleep parameters[a]	Baseline	After lacosamide	Change from baseline (95% CI)
Polysomnographic findings[b]			
WASO, min	23.50 (8–75.5)	13.50 (4.5–144.5)	−6.00 (range: −38 to 77.5) $p = 0.1074$
Sleep efficiency, %	92.71 (70.14–96.93)	93.32 (52.5–98.02)	1.03 (−2.40, 2.40)
Total sleep time, min	419.0 (326.5–460)	423.0 (252–468)	1.50 (−19.00, 16.00)
Sleep onset latency, min	8.0 (0.5–18.5)	5.5 (0–26)	−1.50 (range: −11.5 to 22)
Latency to persistent sleep, min	11.0 (0.5–100)	10.5 (0–84)	−0.5 (range: −98 to 66)
REM latency, min	97.50 (56–271.5)	85.00 (48–279.5)	−18.00 (range: −131 to 122.5)
Stage 1, %	7.41 ± 3.69	7.03 ± 3.40	−0.38 (−1.30, 0.54)
Stage 2, %	52.86 ± 8.27	50.49 ± 8.11	−2.37 (−4.78, 0.04)
Stage 3, %	22.60 ± 8.28	24.95 ± 9.28	2.35 (0.03, 4.67)
Stage REM, %	17.14 ± 3.89	17.54 ± 3.44	0.40 (−1.20, 2.00)
AI, events/h	7.71 ± 4.98	8.030 ± 3.51	0.32 (−1.49, 2.13)
AHI, events/h	0.79 ± 0.98	0.92 ± 0.72	0.14 (−0.33, 0.60)
PLMI, events/h	2.19 ± 3.09	1.52 ± 3.13	−0.68 (−2.08, 0.73)
Subject-rated			
ESS, global score	5.5 ± 3.2	6.1 ± 4.1	0.6 (−0.57, 1.77)
PSQI, total score	4.4 ± 2.5	4.1 ± 1.8	−0.3 (−1.23, 0.67)

AHI, apnea-hypopnea index; AI, arousal index; CI, confidence interval; ESS, Epworth sleepiness scale; PLMI, periodic limb movement index; PSQI, Pittsburgh sleep quality inventory; REM, rapid eye movement; WASO, wake after sleep onset.
[a] Data are presented as median (range) for WASO, sleep efficiency and total sleep time or mean ± SD unless otherwise indicated.
[b] Each overnight PSG was recorded for a minimum of 7 h and a maximum of 8 h.

Table 3
Incidence of treatment-emergent adverse events, safety set.

n (%)	$N = 27$
Any treatment-emergent adverse event	13 (48.1)
Serious treatment-emergent adverse event	1[a] (3.7)
Discontinuations due to treatment-emergent adverse event[b]	0
Treatment-emergent adverse events occurring in >1 subject	
Affect lability	3 (11.1)
Headache	3 (11.1)
Somnolence	3 (11.1)
Dizziness	2 (7.4)
Feeling abnormal	2 (7.4)
Non-cardiac chest pain	2 (7.4)

[a] A serious adverse event of eosinophil count increased (no symptoms reported) was reported for 1 subject; however, no protocol-defined seriousness criteria were met.
[b] One subject discontinued due to adverse events of increased alanine aminotransferase and aspartate aminotransferase levels, which occurred prior to treatment with lacosamide, but the event was not treatment-emergent since no study drug had been taken at the time of elevation.

the event is not treatment-emergent since no study drug had been taken at the time of elevation. Another subject withdrew consent after 7 days of treatment with lacosamide 100 mg/day. One treatment-emergent adverse event of bradycardia was reported in a subject (an athlete) who also had a pre-treatment finding of bradycardia. Bradycardia was detected by ECG and reported as not related to the study drug, and the lacosamide dose was not changed due to the bradycardia.

Overall, there were no clinically relevant changes in mean laboratory parameters, vital signs, ECG measurements, or neurological findings. No subjects reported having suicidal ideation or behavior as assessed by the Columbia-suicide severity rating scale.

4. Discussion

The results of the current study indicate that lacosamide 300 mg/day did not negatively impact or substantially change any objective sleep measures assessed by PSG, including WASO and other sleep parameters. Moreover, since scores on the ESS and PSQI were not significantly different after lacosamide treatment as compared with baseline, no meaningful change was noted in subject-rated daytime sleepiness or sleep quality. Overall, lacosamide 300 mg/day was well tolerated and the safety profile was consistent with that seen in other studies in healthy subjects.[31–33] These results are consistent with other evidence that lacosamide has a good tolerability profile.[22–24,34,35]

The impact that AEDs can have on sleep in patients with epilepsy is well documented, although results vary widely based on the agent, whether acute or long-term effects were evaluated, disease severity, and use of concomitant medications.[1,3–5] In general, older AEDs such as benzodiazepines, barbiturates, and phenytoin have a demonstrated negative impact on sleep parameters, such as a reduction in the amount of time spent in REM sleep and an increase in subject-reported daytime sleepiness.[3,4] Acute detrimental effects of carbamazepine such as increased sleep fragmentation and reduced time spent in REM sleep have been reported, but these are no longer present when sleep was evaluated after 1 month of carbamazepine treatment.[7] Fewer sleep-related side effects are seen with newer AEDs, albeit some effects have been noted with conflicting results. Some second-generation AEDs, such as gabapentin and pregabalin, enhance slow wave sleep.[4] Levetiracetam data are conflicting, generally showing no major effects on objective measures of sleep, but potentially leading to some consolidation of sleep.[36–38]

Many variables impact quality of life in patients with epilepsy, and sleep disturbance and poor quality sleep are known to have a negative impact, but often go unrecognized in a clinical setting.[15,16,39] For example, one survey of patients with epilepsy found that 16.9% of respondents reported excessive daytime sleepiness, 28.2% reported obstructive sleep apnea, and 24.6% reported insomnia, all of which were associated with significant reductions on the quality of life in epilepsy inventory.[16] No data reporting how physicians evaluate or consider sleep when treating epilepsy have been published to date.

The lack of significant impact on subjective sleep parameters noted in the current study is consistent with results from a recent 10-patient open-label study, which indicated that adding lacosamide to an existing treatment regimen for refractory focal epilepsy did not significantly affect self-reported sleep quality or daytime sleepiness.[40] These data suggest that our observations may extend to subjective assessments of sleep in patients with epilepsy. Further study in patients with different types of epilepsy should be conducted to assess whether lacosamide has any impact on objective or subjective sleep parameters, including arousals, stage

shifts and autonomic activity. It would also be useful to assess if lacosamide treatment has any beneficial effects on sleep, such as reducing sleep fragmentation due to reducing nocturnal seizures.

One limitation of this study is that this was an open-label study. Several reports have demonstrated a significant expectation effect on subjective and objective sleep parameters in individuals with insomnia, as well as in healthy subjects.[41–43] However, it is unlikely this occurred in the current study, as no significant positive or negative effects were seen in any of the sleep parameters.

In conclusion, results of the current study indicate that lacosamide does not significantly affect sleep parameters in healthy subjects and is associated with a generally low incidence of intolerable adverse effects. To date, this is the first formal evaluation of the effects of lacosamide on sleep in healthy subjects. Further investigations to assess effects of lacosamide on sleep parameters in patients with epilepsy are required given their potential impact on quality of life and seizure control.

Conflict of interest statement

J. Douglas Hudson received compensation for speaking and serving on an advisory board for UCB Pharma and Jazz Pharmaceuticals. Jeffrey T. Guptill consults for UCB Pharma on projects unrelated to this study. William Byrnes, Stephen L. Yates, Paulette Williams, and O'Neill D'Cruz are employees of UCB Pharma.

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